Clinical trial results:
Interventional, Open-Label, Flexible-Dose, Long-Term Safety Extension Study of Lu AF11167 in Patients with Schizophrenia

Summary

EudraCT number	2018-002708-15
Trial protocol	LV BG DE PL CZ
Global end of trial date	14 September 2020

Results information

Result version number	v1 (current)
This version publication date	11 September 2021
First version publication date	11 September 2021

Trial information

Trial identification

Sponsor protocol code	17972B

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03929497
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	H. Lundbeck A/S
Sponsor organisation address	Otilliavej 9, Valby, Denmark, 2500
Public contact	LundbeckClinicalTrials@lundbeck.com, H. Lundbeck A/S, +45 36301311, LundbeckClinicalTrials@lundbeck.com
Scientific contact	LundbeckClinicalTrials@lundbeck.com, H. Lundbeck A/S, +45 36301311, LundbeckClinicalTrials@lundbeck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 September 2020
Global end of trial reached?	Yes
Global end of trial date	14 September 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to evaluate the long-term safety and tolerability of doses (2 or 4 milligrams [mg]/day) of Lu AF11167 in participants with schizophrenia during the 24-week treatment period.

Protection of trial subjects:

This study was conducted in compliance with Good Clinical Practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 April 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 41
Country: Number of subjects enrolled	Estonia: 14
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Latvia: 1
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Ukraine: 33
Worldwide total number of subjects	96
EEA total number of subjects	63

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	96
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This is a flexible-dose extension study in participants with schizophrenia who had participated and completed Study 17972A (NCT03793712, EudraCT number: 2018-001581-42). The study design included a 24-week Open-Label Treatment Period and a 2-week Safety Follow-up Period.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Lu AF11167 2 or 4 mg/day

Arm description:

Participants received Lu AF11167 tablet orally once daily at a starting dose of 2 mg/day. Based on the investigator's clinical judgement, the dose was increased to 4 mg/day. If this dose was not tolerated, the dose was reduced to 2 mg/day once daily at any time during the study. Total treatment duration was 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Lu AF11167
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

Lu AF11167 was administered per dose and schedule specified in the arm description.

Number of subjects in period 1	Lu AF11167 2 or 4 mg/day
Started	96
Received at least 1 dose of study drug	96
Completed	36
Not completed	60
Consent withdrawn by subject	3
Adverse event, non-fatal	2
Other than specified	54
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Lu AF11167 2 or 4 mg/day

Reporting group description:

Participants received Lu AF11167 tablet orally once daily at a starting dose of 2 mg/day. Based on the investigator's clinical judgement, the dose was increased to 4 mg/day. If this dose was not tolerated, the dose was reduced to 2 mg/day once daily at any time during the study. Total treatment duration was 24 weeks.

Reporting group values	Lu AF11167 2 or 4 mg/day	Total	
Number of subjects	96	96	
Age Categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 43.06 ± 9.34	 -	
Gender Categorical Units: Subjects			
Female	36	36	
Male	60	60	

End points

End points reporting groups

Reporting group title	Lu AF11167 2 or 4 mg/day

Reporting group description:

Participants received Lu AF11167 tablet orally once daily at a starting dose of 2 mg/day. Based on the investigator's clinical judgement, the dose was increased to 4 mg/day. If this dose was not tolerated, the dose was reduced to 2 mg/day once daily at any time during the study. Total treatment duration was 24 weeks.

Primary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs)[1]

End point description:

An adverse event (AE) was any untoward medical occurrence in a participant administered a medicinal product and which did not necessarily have a causal relationship with the treatment. An AE could therefore be any unfavourable and unintended sign (including clinically significant out-of-range values from relevant tests, such as clinical safety laboratory tests, vital signs, electrocardiograms [ECGs]), symptom, or disease temporally associated with the use of a medicinal product, regardless of whether it was considered related to the medicinal product. TEAE was an AE that started or increased in intensity on or after the date of first dose of study drug in this study. A summary of other non-serious AEs and all SAEs, regardless of causality is located in the 'Reported AE section'. All-patients-treated set (APTS) included all enrolled participants who took at least 1 dose of Lu AF11167 in Study 17972B.

End point type	Primary

End point timeframe:

Baseline (Day 0) up to Week 26

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The analysis was descriptive in nature.

End point values	Lu AF11167 2 or 4 mg/day			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: participants	38			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Brief Negative Symptom Scale (BNSS) Total Score at Week 24

End point title	Change From Baseline in Brief Negative Symptom Scale (BNSS) Total Score at Week 24

End point description:

The BNSS is a brief clinician rating scale, intended to measure negative symptoms. It consists of 13 items organized into 6 subscales: anhedonia, distress, asociality, avolition, blunted affect, and alogia. The items score the impairment. Items 1 to 4 were rated from 0 (Normal) to 6 (Extremely severe) and items 5 to 13 were rated from 0 (No impairment) to 6 (Severe deficit). The BNSS total score was calculated by summing the 13 individual items. The BNSS total scores range from 0 to 78. Full analysis set (FAS) included all enrolled participants who took at least 1 dose of the Lu AF11167 in Study 17972B

and who had a valid baseline assessment and at least 1 valid post-baseline assessment of the BNSS total score. 'Overall number of participants analyzed' = participants analyzed for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Lu AF11167 2 or 4 mg/day			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: units on a scale				
arithmetic mean (standard deviation)	-5.24 (± 6.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Positive and Negative Syndrome Scale (PANSS) Marder Factor Negative Symptoms Factor Score at Week 24

End point title	Change From Baseline in Positive and Negative Syndrome Scale (PANSS) Marder Factor Negative Symptoms Factor Score at Week 24

End point description:

PANSS is a clinician rated scale designed to measure severity of psychopathology in adult participants with schizophrenia, schizoaffective disorders and other psychotic disorders. It includes 3 sub-scales and 30 items: 7 items for positive scale (for example: delusions, conceptual disorganization, and hallucinatory behaviour), 7 items for negative scale (for example: blunted affect, emotional withdrawal, and poor rapport) and 16 items for general psychopathology scale (for example: somatic concern, anxiety, and guilt feelings). Each item is rated from 1 (no symptoms) to 7 (extremely severe symptom). PANSS total score: sum of all items and ranges from 30 to 210. Subscale scores: sum of items within each subscale. FAS: all enrolled participants who took at least 1 dose of the Lu AF11167 in Study 17972B and who had a valid baseline and at least 1 valid post-baseline assessment of the BNSS total score. 'Overall number of participants analyzed' = participants analyzed for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Lu AF11167 2 or 4 mg/day			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: units on a scale				
arithmetic mean (standard deviation)	-2.53 (± 2.42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PANSS Negative Subscale Score at Week 24

End point title	Change From Baseline in PANSS Negative Subscale Score at Week 24

End point description:

PANSS is a clinician rated scale designed to measure severity of psychopathology in adult participants with schizophrenia, schizoaffective disorders, and other psychotic disorders. It includes 3 sub-scales and 30 items: 7 items for positive scale (for example: delusions, conceptual disorganization, and hallucinatory behaviour), 7 items for negative scale (for example: blunted affect, emotional withdrawal, and poor rapport) and 16 items for general psychopathology scale (for example: somatic concern, anxiety, and guilt feelings). Each item is rated from 1 (no symptoms) to 7 (extremely severe symptom). Subscale scores: sum of items within each subscale. FAS: all enrolled participants who took at least 1 dose of the Lu AF11167 in Study 17972B and who had a valid baseline and at least 1 valid post-baseline assessment of the BNSS total score. 'Overall number of participants analyzed' = participants analyzed for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Lu AF11167 2 or 4 mg/day			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: units on a scale				
arithmetic mean (standard deviation)	-2.63 (± 2.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Global Impression — Schizophrenia Severity of Illness (CGI-SCH-S) Negative Symptoms Score at Week 24

End point title	Change From Baseline in Clinical Global Impression — Schizophrenia Severity of Illness (CGI-SCH-S) Negative Symptoms Score at Week 24

End point description:

The CGI-SCH is a clinician-rated scale to assess global illness severity and degree of change in participants with schizophrenia. For both the global illness severity and degree of change, the CGI-SCH consists of 4 different groups of symptoms (positive, negative, cognitive, and depressive) and the overall severity of the disorder. The CGI-SCH severity of illness category symptoms and overall severity were rated on a 7-point scale ranging from 1 (normal - not ill) to 7 (among the most severely ill). Each single rating (conditions of severity and degree of improvement) and overall ratings of severity and improvement were scored independently, and no total score was derived. FAS: all enrolled participants who took at least 1 dose of the Lu AF11167 in Study 17972B and who had a valid baseline and at least 1 valid post-baseline assessment of the BNSS total score. 'Overall number of participants analyzed' = participants analyzed for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Lu AF11167 2 or 4 mg/day			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: units on a scale				
arithmetic mean (standard deviation)	-0.26 (± 0.45)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression — Schizophrenia Degree of Change (CGI-SCH-DC) Negative Symptoms Score at Week 24

End point title	Clinical Global Impression — Schizophrenia Degree of Change (CGI-SCH-DC) Negative Symptoms Score at Week 24

End point description:

The CGI-SCH is a clinician-rated scale to assess global illness severity and degree of change in participants with schizophrenia. For both the global illness severity and degree of change, the CGI-SCH consists of 4 different groups of symptoms (positive, negative, cognitive, and depressive) and the overall severity of the disorder. In the CGI-SCH degree of change category symptoms and overall severity were rated on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Each single rating (conditions of severity and degree of improvement) and overall ratings of severity and improvement were scored independently, and no total score was derived. FAS: all enrolled participants who took at least 1 dose of the Lu AF11167 in Study 17972B and who had a valid baseline and at least 1 valid post-baseline assessment of the BNSS total score. 'Overall number of participants analyzed' = participants analyzed for this endpoint.

End point type	Secondary

End point timeframe:

Week 24

End point values	Lu AF11167 2 or 4 mg/day			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: units on a scale				
arithmetic mean (standard deviation)	3.50 (± 0.56)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With a CGI-SCH-DC Negative Symptoms Response at Week 24

End point title	Number of Participants With a CGI-SCH-DC Negative

	Symptoms Response at Week 24

End point description:

CGI-SCH is a clinician-rated scale to assess global illness severity and degree of change in participants with schizophrenia. For both global illness severity and degree of change, CGI-SCH consists of 4 groups of symptoms (positive, negative, cognitive, and depressive) and overall severity of disorder. In CGI-SCH degree of change category symptoms and overall severity were rated on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Each single rating (conditions of severity and degree of improvement) and overall ratings of severity and improvement were scored independently, and no total score was derived. CGI-SCH-DC negative symptoms response defined as CGI-SCH-DC negative symptoms score of 1 or 2. FAS: all enrolled participants who took at least 1 dose of Lu AF11167 in Study 17972B and who had a valid baseline and at least 1 valid post-baseline assessment of BNSS total score. 'Overall number of participants analyzed'=participants analyzed for this endpoint.

End point type	Secondary

End point timeframe:

Week 24

End point values	Lu AF11167 2 or 4 mg/day			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: participants	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline (Day 0) up to Week 26	
Adverse event reporting additional description:	
APTS included all enrolled participants who took at least 1 dose of Lu AF11167 in Study 17972B.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Lu AF11167 2 or 4 mg/day
Reporting group description:	
Participants received Lu AF11167 tablet orally once daily at a starting dose of 2 mg/day. Based on the investigator's clinical judgement, the dose was increased to 4 mg/day. If this dose was not tolerated, the dose was reduced to 2 mg/day once daily at any time during the study. Total treatment duration was 24 weeks.	

Serious adverse events	Lu AF11167 2 or 4 mg/day		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 96 (1.04%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Haemorrhagic stroke			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Lu AF11167 2 or 4 mg/day		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 96 (17.71%)		
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 96 (12.50%)		
occurrences (all)	18		
Psychiatric disorders			

Agitation subjects affected / exposed occurrences (all)	6 / 96 (6.25%) 7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2018	This amendment was prepared to update the heart-rate corrected QT interval using Fridericia's correction formula (QTcF) withdrawal criteria, to update the Cogstate Schizophrenia Cognitive Battery and timepoint of Entry/Exit interviews, and to provide clarifications and corrections to the protocol.
11 May 2020	This amendment was prepared to add the United States as a participating country.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated based on the interim analysis for futility in the lead-in Study 17972A.

Notes: